



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/DK92/00187 (22) International Filing Date: 16 June 1992 (16.06.92) (30) Priority data: 1165/91 17 June 1991 (17.06.91) DK (71) Applicant (for all designated States except US): FARMAC-EUTISK LABORATORIUM FERRING A/S [DK/DK]; Indertofte 5, DK-2720 Vanløse (DK). (72) Inventor; and (75) Inventor/Applicant (for US only): HALSKOV, Søren [DK/DK]; Parcelvej 111, DK-2830 Virum (DK). (74) Agent: HOFMAN-BANG & BOUTARD A/S; Adelgade 15, DK-1304 Copenhagen K (DK).</p>	<p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published <i>With international search report.</i> <i>With amended claims.</i> <i>In English translation (filed in Danish).</i></p>	
<p>(54) Title: A PROCESS FOR PRODUCING SUPPOSITORIES BY COMPRESSION AND SUPPOSITORIES OBTAINED BY THE PROCESS</p>		
<p>(57) Abstract</p> <p>Suppositories which may have a considerably higher content of an active drug than ordinary suppositories, are produced by compressing a suppository mass, which contains a considerable amount of a polyethylene glycol having a molecular weight of at least 4000, preferably 6000. The polyethylene glycol constitutes 20-50 % by weight of the suppository mass, which moreover contains microcrystalline cellulose and/or other additives common in the production of drugs. The obtained suppositories are more convenient to store and use, easier to produce and considerably more concentrated with respect to active substance (up to 75 % by weight) than traditional melt-moulded suppositories.</p>		

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A process for producing suppositories by compression and
suppositories obtained by the process

5 The present invention concerns a special process for pro-
ducing suppositories by compression, and the process of
the invention is characterized by producing a suppository
mixture granulate containing a considerably greater amount
of active drug than ordinary suppositories as well as 20-
50% by weight of a polyethylene glycol having an average
10 molecular weight of at least 4000, and producing the sup-
positories in the same manner as tablets, i.e. by compres-
sion, instead of by moulding. The invention moreover con-
cerns the suppositories obtained by the process which have
a considerably higher percentual content of active drug
15 than ordinary suppositories.

As will be known, suppositories are drugs intended for
insertion into the rectum. They contain the active drug in
a dosed amount and are produced by pressing, moulding or
20 compression. They can also be produced in the form of cap-
sules for controlled release of the active substance.

Ordinarily suppositories are produced by moulding, the
produced mass being melted using the least possible amount
of heat, and then the liquid mass is poured into moulds
25 having the desired nominal capacity.

The suppositories produced by moulding are oblong and
smooth, and they have a uniform appearance. Melting is in-
30 tended to provide a uniform distribution of the drug in
the basic mass, which, however, can be difficult to obtain
because of sedimentation during hardening.

However, traditional moulding is a time-consuming and slow
35 process which involves considerable costs. Moulded suppo-

sitories also have the drawback that too strong heating of certain suppository basic masses result in unstable modifications with a considerably reduced solidification point.

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It is well-known to use polyethylene glycols having average molecular weights of 4000-6000 or above as the main component in the basic mass for suppositories produced by traditional melting and moulding. Thus, the DE Offenlegungsschrift 2 248 777 describes melt-moulded indomethacin suppositories whose basic mass contains such polyethylene glycols.

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An object of the invention is to provide a process enabling the production of suppositories having a high content of active drug, which are partly more convenient to store and are partly more convenient to use and easier and cheaper to produce than traditional melt-moulded suppositories.

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This is achieved by the process of the invention which is characterized by the subject-matter stated in the characterizing portion of claim 1.

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It has previously been attempted to produce suppositories by compression or pressing, i.e. by traditional tableting methods. However, these suppositories tend to form irregular rough surfaces, which makes them unpleasant to use for the patient. Moreover, in such a production method it has been found impossible to dose the drug in so high doses as is often desirable owing to the prescribed treatment.

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Thus, the EP publication 111 137 describes suppositories containing the drug indomethacin in a base consisting of polyethylene glycol having an average molecular weight of

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up to 35,000. It is stated that the content of the active drug may be up to 50% by weight, but preferably the content is 2-40% by weight and in particular 2-26% by weight. All the examples in the publication concern rectal tablets having a content of indomethacin of 2.8 - 5.8% by weight and rectal capsules having a content of indomethacin of 5.25 - 10.5% by weight, i.e. rather low concentrations. Further, the suppositories thus known contain quite high amounts of polyethylene glycols, typically 1600-1730 mg per unit, which is a drawback, because it has been found that a content of polyethylene glycols in suppositories of 1 - 1.5 g per unit may cause bowel disorders.

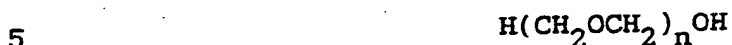
It has now surprisingly been found that a composition which can easily be compressed to suppositories by an ordinary tableting method can be obtained by using a suitable amount, more particularly 20-50% by weight of a polyethylene glycol having an average molecular weight of at least 4000 in the suppository basic mass. The use of such a polyethylene glycol in the basic mass results in suppositories having a uniform appearance and having an extremely smooth and regular surface, which is moreover sufficiently slippery for the suppository to be inserted without difficulty. It is moreover possible in such suppositories to incorporate up to 75% by weight of active drug, which is far above normal.

Polyethylene glycols, more particularly mixtures of condensation polymers of ethylene oxide and water, are also called "macrogols". Macrogols having average molecular weights of 200-700 are liquids, while macrogols having average molecular weights above 1000 vary in consistence from soft oily substances to hard wax-like solid substances. The average molecular weight is stated as a number after the name. "Macrogol 6000", which it is preferred to use according to the invention, thus has an ave-

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rage molecular weight of about 6000.

The macrogols have the general formula



where n is greater than or equal to 4. In "Macrogol 6000" n has an average value of between 158 and 204. It is a white or cream-coloured solid wax-like substance which is in the form of a powder or flakes. The melting point is 56-63°C, i.e. considerably above the body temperature. Mixtures of various polyethylene glycols having melting points above the body temperature have frequently been used as a base in suppositories from which the drug is released by dissolution.

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Since the melting points of the macrogols increase with increasing average molecular weight, macrogols having high average molecular weights, such as "Macrogol 6000", have not previously been a natural choice as a suppository base material.

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Mixing a granulate of the drug with "Macrogol 6000" and compressing the mixture to suppositories by a method which is known per se for the production of tablets for oral administration provide the following advantages:

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- 1) The suppositories do not melt under normal temperature conditions, but only at about 60°C.
 - 2) The suppositories are cheaper to produce.
 - 3) The drug can be incorporated in very high concentrations and is considerably easier to dose uniformly.
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- 4) The product is more convenient and more pleasant to use for the patient.
- 5) Avoidance of drug decomposition during the heating which is necessary in traditional moulding of suppositories.
- 6) It is easier to obtain and maintain a homogeneous mixture, and the risk of sedimentation is eliminated.

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All active drugs which lend themselves for rectal administration may be incorporated in the suppositories produced according to the invention. One of the interesting drugs in this respect is 5-aminosalicylic acid (5-ASA), which is used particularly for the treatment of colitis ulcerosa and Crohn's disease, but which has moreover been found to be of interest for the production of suppositories for treatment of hemorrhoids. Suppositories containing 5-aminosalicylic acid are known e.g. from the EP patent application 83 775, these suppositories being produced by moulding and containing max. 500 mg of 5-aminosalicylic acid per dose unit. The suppositories of the invention may contain considerably larger amounts of 5-ASA, which is absolutely an advantage for the patient.

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An example of the many active drugs which may be used is steroids for various applications.

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In addition to a polyethylene glycol or a mixture of polyethylene glycols having an average molecular weight of at least 4000, preferably "Macrogol 6000", in an amount of 20-50% by weight, the suppositories produced according to the invention contain microcrystalline cellulose and/or other additives common in the production of drugs. These additives and the active drug together amount to 45-75% based on the gross weight of the suppositories. Finally,

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the suppositories contain one or more of the substances talc, magnesium stearate and polyvinyl pyrrolidone in an amount of 2-5% by weight.

5 The suppositories are typically compressed to symmetrical units having an approximately elliptic longitudinal section, i.e. the two ends are uniform (in contrast to the ordinary "torpedo-shape" where one end is pointed while the other is blunt).

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The following example illustrates the invention:

EXAMPLE

15 A suppository basic mass for the production of 1000 suppositories consists of the following ingredients:

	"Macrogol 6000"	572 g
	Microcrystalline cellulose	
20	and active drug	1000 g
	Magnesium stearate	4 g
	Talc	4 g
	Polyvinyl pyrrolidone	
	+ ethanol (1:19)	q.s.

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A granulate is made from the microcrystalline cellulose, the active drug, e.g. 5-aminosalicylic acid (5-ASA) and the mixture of polyvinyl pyrrolidone and ethanol.

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The resulting granulate is mixed with "Macrogol 6000", and then magnesium stearate and talc are added.

The granulate can then be compressed to suppositories in a tableting machine in a manner known per se.

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P a t e n t C l a i m s :

5 1. A process for producing suppositories by compression,
c h a r a c t e r i z e d by producing a suppository mix-
ture granulate containing a considerably larger amount of
active drug than ordinary suppositories as well as 20-50%
by weight of a polyethylene glycol having an average mole-
10 cular weight of at least 4000, and then compressing the
produced mass to suppositories by a method known per se
for the production of tablets.

15 2. A process according to claim 1, c h a r a c t e r -
i z e d by producing a suppository mass having the
following composition:

polyethylene glycol:	20-50%
active drug	
as well as microcrystalline cellulose	
20 and/or other additives common in the	
production of drugs:	45-75%, preferably
	at least 50%
talc, magnesium stearate and/or	
25 polyvinyl pyrrolidone:	2-5%

the stated percentages being percentages by weight.

30 3. A process according to claim 1 or 2, c h a r a c -
t e r i z e d in that the polyethylene glycol used has an
average molecular weight of 6000.

35 4. A process according to any of the preceding claims,
c h a r a c t e r i z e d in that the polyethylene glycol
used is selected from "Macrogol 4000", "Macrogol 6000" and
mixtures thereof.

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5. Suppositories, characterized in that they are produced by a process according to any of claims 1-4.

6. Suppositories according to claim 5, characterized in that they have the following composition:

polyethylene glycol having an average molecular weight of

at least 4000:

20-50%

active drug

as well as microcrystalline cellulose

and/or other additives common in the

production of drugs:

45-75%, preferably

at least 50%

talc, magnesium stearate and/or

polyvinyl pyrrolidone:

2-5%

the stated percentages being percentages by weight.

7. Suppositories according to claim 5 or 6, characterized in that the polyethylene glycol used is "Macrogol 6000".

8. Suppositories according to any of claims 5-7, characterized in that they contain 5-aminosalicylic acid (5-ASA) as an active drug in an amount of up to 75% of the gross weight of the product.

9. Suppositories according to any of claims 5-7, characterized in that they contain a steroid as an active drug.

AMENDED CLAIMS

[received by the International Bureau on 23 October 1992 (23.10.92);
original claims 1-9 replaced by amended claims 1-8 (2 pages)]

1. A process for producing suppositories by compression,
5 c h a r a c t e r i z e d by producing a suppository mixture granulate containing 50-75% active drug as well as optionally microcrystalline cellulose and/or other additives common in the production of drugs, 2-5% talc, magnesium stearate and/or polyvinyl pyrrolidone as well as 20-
10 50% by weight of a polyethylene glycol having an average molecular weight of at least 4000, and compressing the produced mass to suppositories by a method known per se for the production of tablets.
- 15 2. A process according to claim 1, c h a r a c t e r i z e d in that the polyethylene glycol used has an average molecular weight of 6000.
- 20 3. A process according to claim 1 or 2, c h a r a c t e r i z e d in that the polyethylene glycol used is selected from "Macrogol 4000", "Macrogol 6000" and mixtures thereof.
- 25 4. Suppositories, c h a r a c t e r i z e d in that they are produced by a process according to any of claims 1-3.
5. Suppositories according to claim 4, c h a r a c t e r i z e d in that they have the following composition:
30 polyethylene glycol having
an average molecular weight
of at least 4000: 20-50%
active drug
35 as well as microcrystalline
cellulose and/or other

additives common in the production of drugs:	50-75%
talc, magnesium stearate and/or polyvinyl pyrrolidone:	2-5%

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the stated percentages being percentages by weight.

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6. Suppositories according to claim 4 or 5, characterized in that the polyethylene glycol used is "Macrogol 6000".

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7. Suppositories according to any of claims 4-6, characterized in that they contain 5-aminosalicylic acid (5-ASA) as an active drug in an amount of up to 75% of the gross weight of the product.

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8. Suppositories according to any of claims 4-6, characterized in that they contain a steroid as an active drug.

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INTERNATIONAL SEARCH REPORT

International Application No **PCT/DK 92/00187**

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 9/02, A 61 J 3/08											
II. FIELDS SEARCHED <div style="text-align: center;">Minimum Documentation Searched⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20%; padding: 5px;">Classification System</td> <td style="padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="padding: 5px;">IPC5</td> <td style="padding: 5px;">A 61 K; A 61 J</td> </tr> </table>			Classification System	Classification Symbols	IPC5	A 61 K; A 61 J					
Classification System	Classification Symbols										
IPC5	A 61 K; A 61 J										
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸ SE,DK,FI,NO classes as above											
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category *</th> <th style="width: 60%; padding: 5px;">Citation of Document,¹¹ with Indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">DE, A, 2248777 (MERCK & CO. INC.) 19 April 1973, see the whole document --</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-9</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">EP, A2, 0111137 (TROPONWERKE GMBH & CO. KG) 20 June 1984, see the whole document -----</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-9</td> </tr> </tbody> </table>			Category *	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	DE, A, 2248777 (MERCK & CO. INC.) 19 April 1973, see the whole document --	1-9	X	EP, A2, 0111137 (TROPONWERKE GMBH & CO. KG) 20 June 1984, see the whole document -----	1-9
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<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; border: none;"> ¹⁰ Special categories of cited documents: ^{"A"} document defining the general state of the art which is not considered to be of particular relevance ^{"E"} earlier document but published on or after the international filing date ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ^{"O"} document referring to an oral disclosure, use, exhibition or other means ^{"P"} document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; vertical-align: top; border: none;"> ^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"&"} document member of the same patent family </td> </tr> </table>			¹⁰ Special categories of cited documents: ^{"A"} document defining the general state of the art which is not considered to be of particular relevance ^{"E"} earlier document but published on or after the international filing date ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ^{"O"} document referring to an oral disclosure, use, exhibition or other means ^{"P"} document published prior to the international filing date but later than the priority date claimed	^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"&"} document member of the same patent family							
¹⁰ Special categories of cited documents: ^{"A"} document defining the general state of the art which is not considered to be of particular relevance ^{"E"} earlier document but published on or after the international filing date ^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) ^{"O"} document referring to an oral disclosure, use, exhibition or other means ^{"P"} document published prior to the international filing date but later than the priority date claimed	^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention ^{"X"} document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step ^{"Y"} document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. ^{"&"} document member of the same patent family										
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;">Date of the Actual Completion of the International Search 21st September 1992</td> <td style="width: 50%; padding: 5px;">Date of Mailing of this International Search Report 22 -09- 1992</td> </tr> <tr> <td style="padding: 5px;">International Searching Authority SWEDISH PATENT OFFICE</td> <td style="padding: 5px;">Signature of Authorized Officer <i>Anneli Jönsson</i> Anneli Jönsson</td> </tr> </table>			Date of the Actual Completion of the International Search 21st September 1992	Date of Mailing of this International Search Report 22 -09- 1992	International Searching Authority SWEDISH PATENT OFFICE	Signature of Authorized Officer <i>Anneli Jönsson</i> Anneli Jönsson					
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 92/00187**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **28/08/92**. The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A- 2248777	73-04-19	AT-B- 336188 AU-B- 472229 AU-D- 4708472 BE-A- 789726 CA-A- 985625 FR-A-B- 2158209 GB-A- 1384760 NL-A- 7212626 SE-B-C- 384134 US-A- 3849549	77-04-25 76-05-20 74-04-04 73-04-05 76-03-16 73-06-15 75-02-19 73-04-10 76-04-26 74-11-19
EP-A2- 0111137	84-06-20	DE-A- 3241263 JP-A- 59101420	84-05-10 84-06-12